Erections

ANATOMICAL OVER VIEW

The average size of the penis is

- flaccid length is 8-9cm
- stretched or erect length is 12-14cm

Gross anatomy of the penis

- corpora cavernosum join beneath pubis to form body of penis
  - incomplete septum distally
  - enclosed by tunica albuginea (outer longitudinal & inner circular fibers)
  - smooth muscle bundles w/in
- distal to bulb, corpus spongiosum tapers & runs on ventral surface of cavernosa, expanding to form glans
  - urethra runs along entire length, starting at perineal membrane
  - urethra is lined proximally by columnar, distally by squamous epithelium
  - may see mucous-secreting glands of Littre
- Buck’s fascia surrounds cavernosal bodies and splits to surround spongiosum ventrally
  - fuses with pubis via suspensory ligament
  - distally it fuses with glans at corona
  - **proximally in perineum it fuses with tunica albuginea and surrounds crura and bulb of spongiosum**
  - penile fracture tears tunica albuginea contained by Buck’s so ecchymosis limited to shaft
  - neurovascular bundles of penis lie DEEP to Buck’s fascia
- **penile skin** is highly elastic and without appendages (hair or glandular elements)
  - **blood supply is independent of the erectle bodies and comes from the external pudendal branches of femoral vessels**
  - rich anastomotic network so penile skin is ideal for mobilization on vascular pedicle

The penis is surrounded by

- penile skin
- dartos fascia } continuous with Scarpa's fascia
- tela subfascialis □ very thin CT layer
- Buck's fascia } continuous with external spermatic fascia
- tunica albuginea

the tunica albuginea covering the corpora cavernosa is formed of 2 layer

□ composed of fibrillar collagen (mostly type 1 and some type 3) + elastin

- inner circular layer } support
  } intracavernous pillars radiate from inner layer to support
  } emissary veins run b/w inner & outer layer, often piercing inner layer obliquely
- outer longitudinal layer } strength layer
  } extends from glans to proximal crura, inserting into inferior pubic rami
  } absent between 5 and 7 o'clock (ventral grove)
  □ weakest area of tunica
  } compresses emissary veins during erection

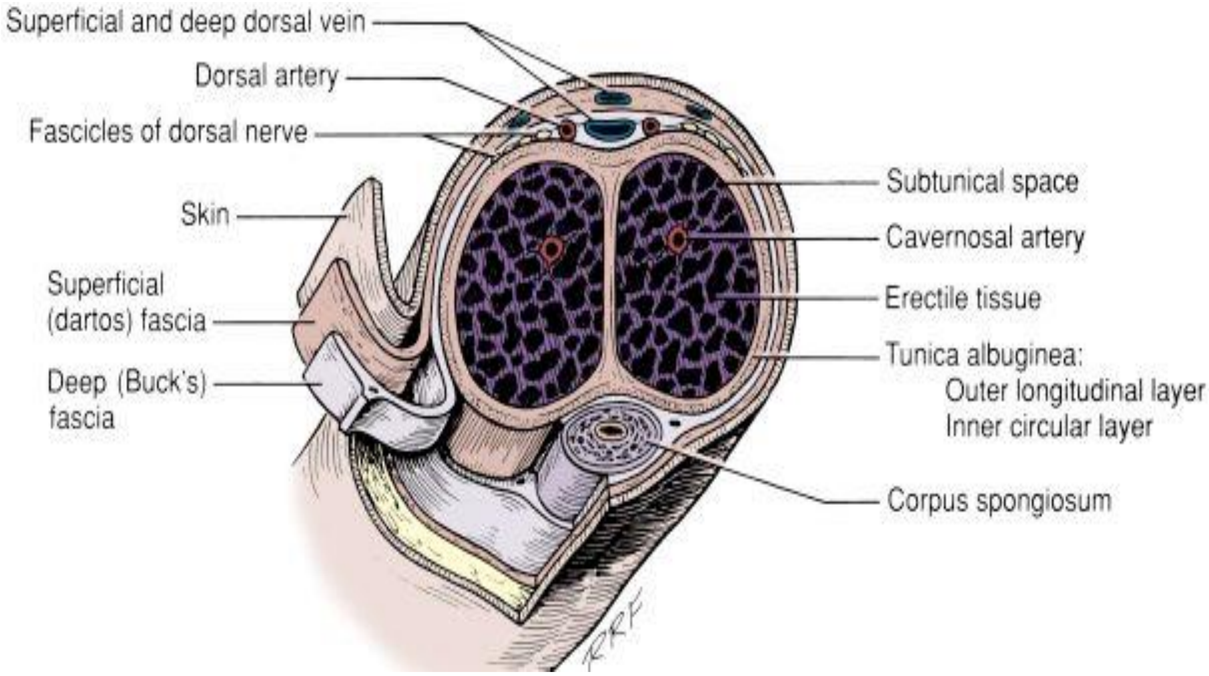
□ corpous spongiosum lacks intracorporeal struts and outer layer

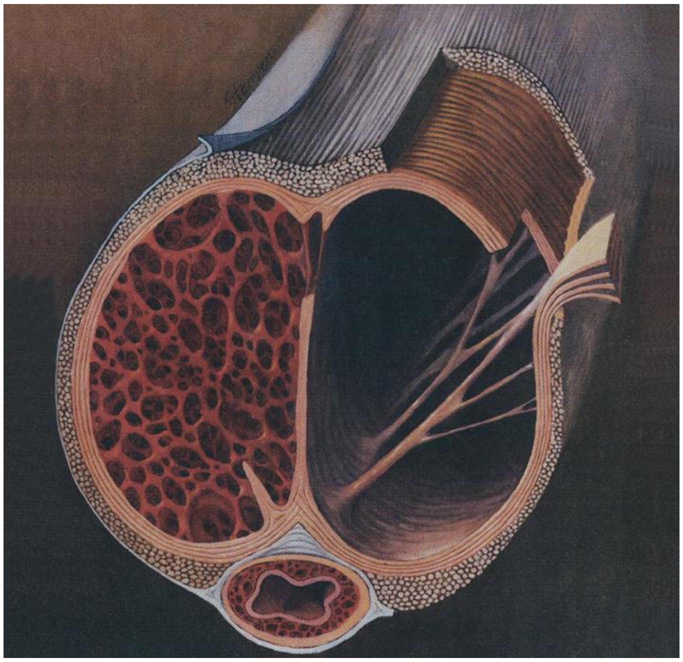
the ligamentous supports of the penis is

1) fundiform ligament } arises from **Colles' fascia**
   } lateral, superficial, and **NOT stuck to tunica albuginea**
2) suspensory ligament } arises from **Buck's fascia**
   } 2 lateral bundles + 1 median bundle and **stuck to tunica**
   □ attaches tunica albuginea of corpora cavernosa to pubis

glands of Tyson

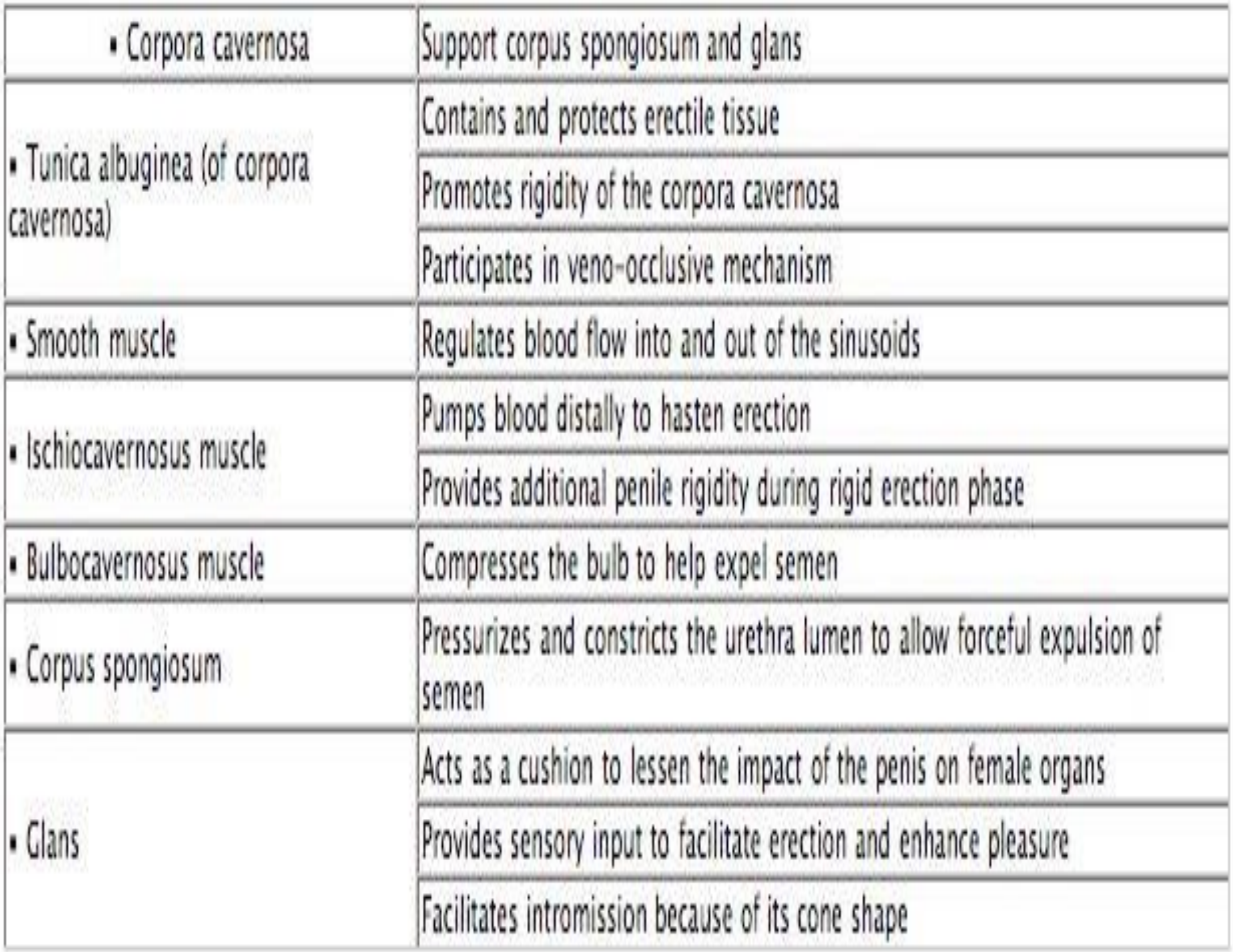
- preputial glands at coronal sulcus that secrete sebaceous material (smegma when mixed with desquamated epithelial cells)





Notice The longitudinal layer is absent in the ventral groove housing the corpus spongiosum

Penile Components and Their Function during Penile Erection



▪ Corpora cavernosa	Support corpus spongiosum and glans
▪ Tunica albuginea (of corpora cavernosa)	Contains and protects erectile tissue
	Promotes rigidity of the corpora cavernosa
	Participates in veno-occlusive mechanism
▪ Smooth muscle	Regulates blood flow into and out of the sinusoids
▪ Ischiocavernosus muscle	Pumps blood distally to hasten erection
	Provides additional penile rigidity during rigid erection phase
▪ Bulbocavernosus muscle	Compresses the bulb to help expel semen
▪ Corpus spongiosum	Pressurizes and constricts the urethra lumen to allow forceful expulsion of semen
▪ Glans	Acts as a cushion to lessen the impact of the penis on female organs
	Provides sensory input to facilitate erection and enhance pleasure
	Facilitates intromission because of its cone shape

blood supply to the penis

- penile skin } **external pudendal** branch off femoral vessels
- penis } int. iliac →int. pudendal →common penile

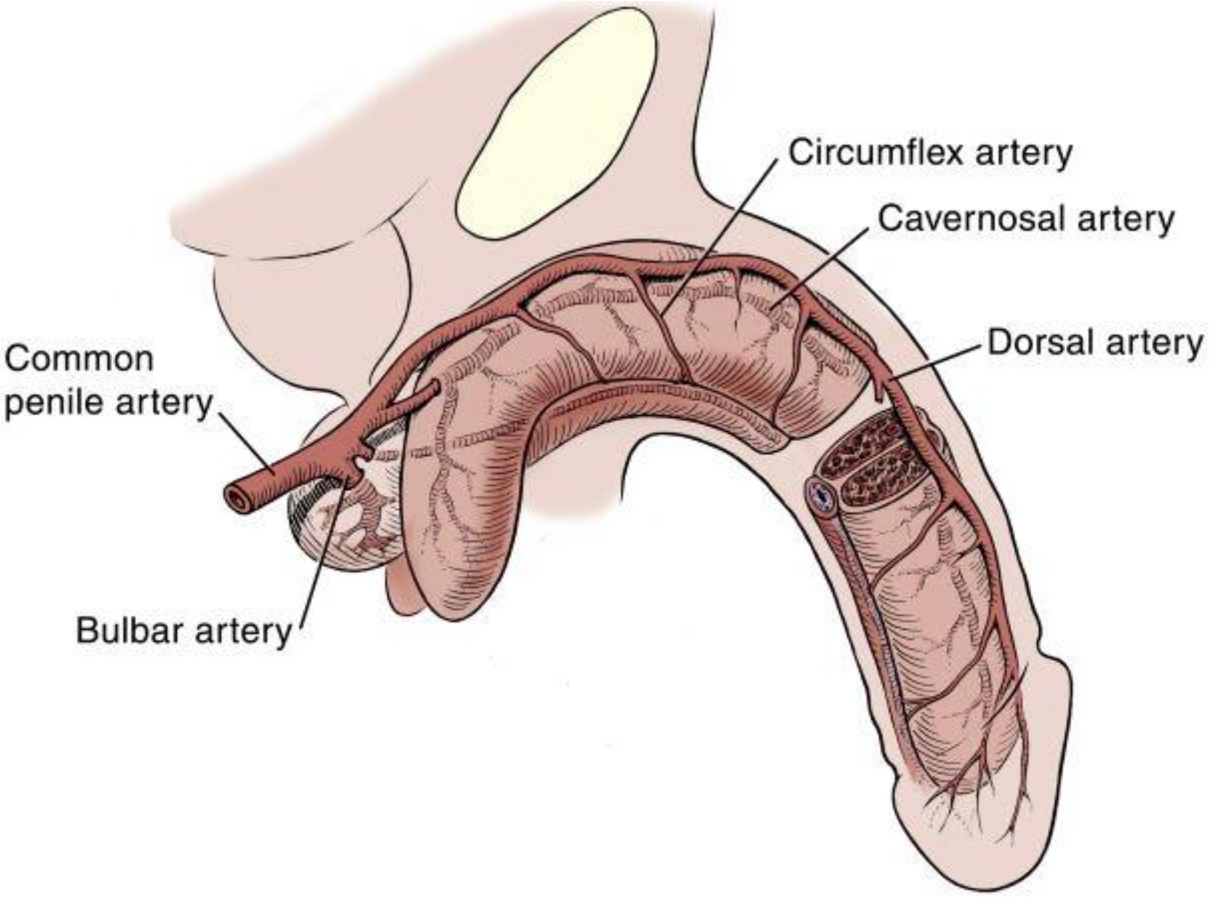
1) **dorsal** → cavernous branches to corpora & circumflex branches to spongiosum & urethra (ends in glans)

2) **cavernosal** →straight and helicine arteries to caverosum

3) **bulbourethral** →spongiosum, urethra, & glans

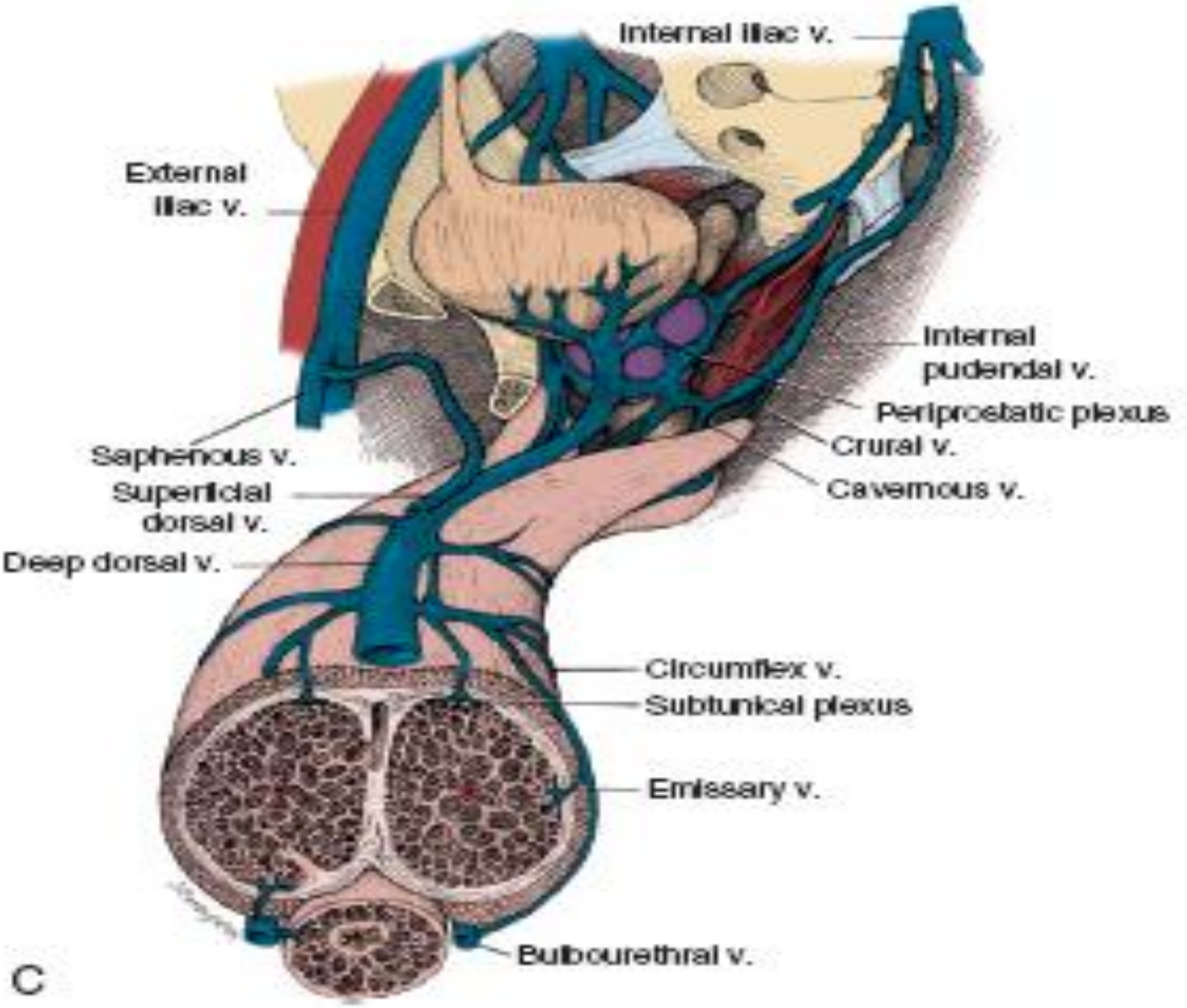
} accessory pudendal artery may also contribute

} other possible accessory arteries →from ext. iliac, obturator, vesical and femoral



venous drainage of the penisall 3 systems can communicate

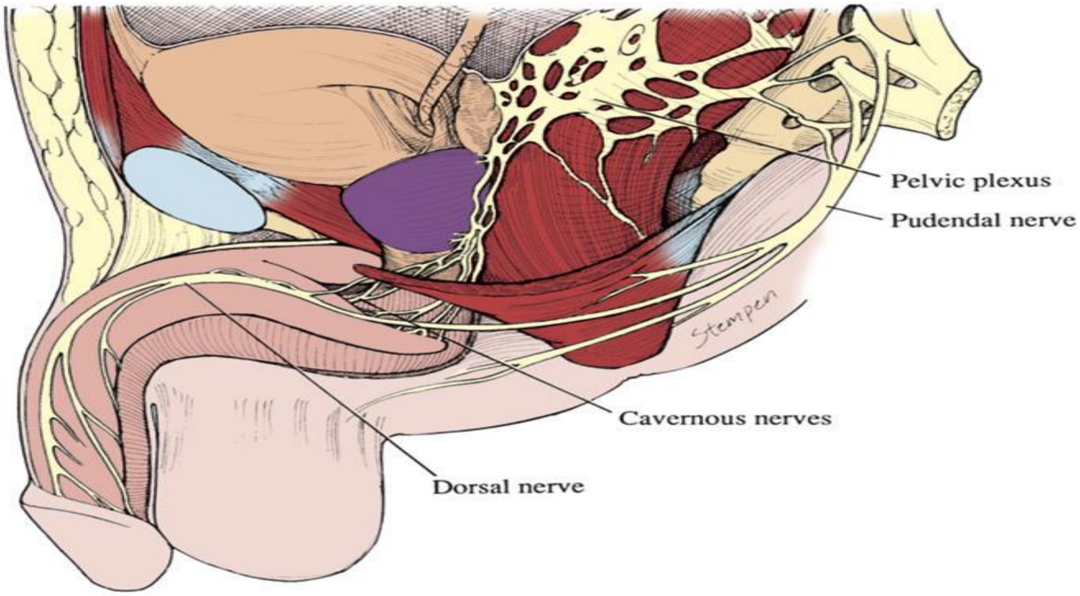
1) superficial (skin)
   - **superficial dorsal vein** →usually drains to **L saphenous vein**
2) intermediate
   - subtunical capillary plexus →emissary veins →circumflex veins →
     → **deep dorsal veins** (w/in Bucks) + periurethral veins →**Santorini's plexus** →vesical plexus →**internal iliacs** veins
3) deep
   - **crural, cavernosal, bulbar veins** → **internal pudendal veins** →internal iliac veins



innervation of the penis

- **somatics** } **pudendal nerve (S2-S4)**
  - ☐ give off inferior rectal, dorsal penile, perineal branches
  - ☐ dorsal penile nerves provide sensation to penis
    - follow dorsal arteries and richly supply glans
    - **run outside pelvis ∴ preserved during pelvic sx**
  - ☐ perineal nerve branches supply ventral penis
  - ☐ also controls contraction of ischiocavernosus (rigid-erection phase) and bulbocavernosus (ejaculation) muscles
- **autonomics** } **cavernosal nerves** innervate corporal bodies (NVB)
  - ☐ come **from pelvic plexus** and enter corporal bodies
  - ☐ **sympathetic tone (T10-L2)** causes detumescence
  - ☐ **parasympathetic activity (S2-S4)** causes erections
    - release NO, acetylcholine, VIP that causes smooth muscle and arterial relaxation
  - } dorsal penile nerve may also have some parasympathetic input

the center of somatomotor penile innervation in the spine is Onuf’s nucleus (S2-S4)



the corpus spongiosum differ from the corpora cavernosa by

- larger sinusoids
- thinner tunica (only inner circular layer)

Physiological over view

changes associated with erections

□ **sinusoidal relaxation + arterial dilation + venous compression**

1) relaxation of smooth muscle
2) dilation of arterioles & arteries by increased blood flow in both diastolic & systolic phases
3) trapping of incoming blood by the expanding sinusoids
4) compression of subtunical venous plexuses between tunica albuginea & peripheral sinusoids

    □ reduces venous outflow

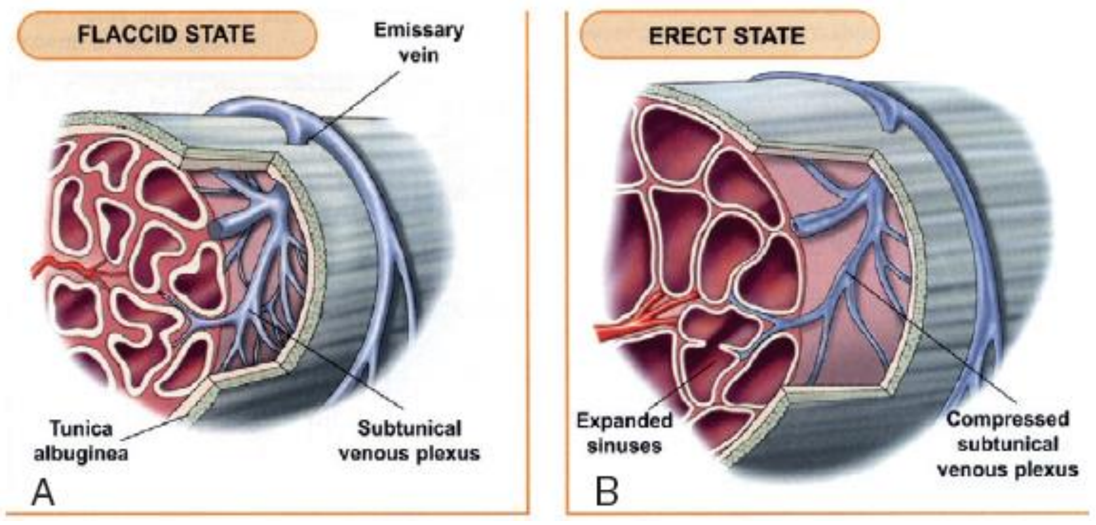
5) stretching of tunica to its capacity

    □ occludes emissary veins b/w inner circular & outer longitudinal layers, further ↓'ing outflow

6) increase in PO2 (to ~90 mmHg) & intracavernous pressure (~100 mmHg)

    □ raises penis to full-erection phase

7) pressure ↑'s more (to several hundred mmHg) w/ ctx of ischiocavernosus m. (rigid-erection phase)



phases of penile erection & detumescence

1) latent dilation of arteries, sinusoidal relaxation and trapping of blood
2) tumescence } compression of subtunical venous plexuses, stretching of tunica to capacity
3) full erection } increase in IC pressure
4) rigid erection } contraction of ischiocavernosus muscle
5) initial detumescence } smooth muscle contraction against closed venous system
   } transient rise in IC pressure
6) slow detumescence } slow reopening of venous channels
7) fast detumescence } fully restored venous outflow capacity

phases of detumescence

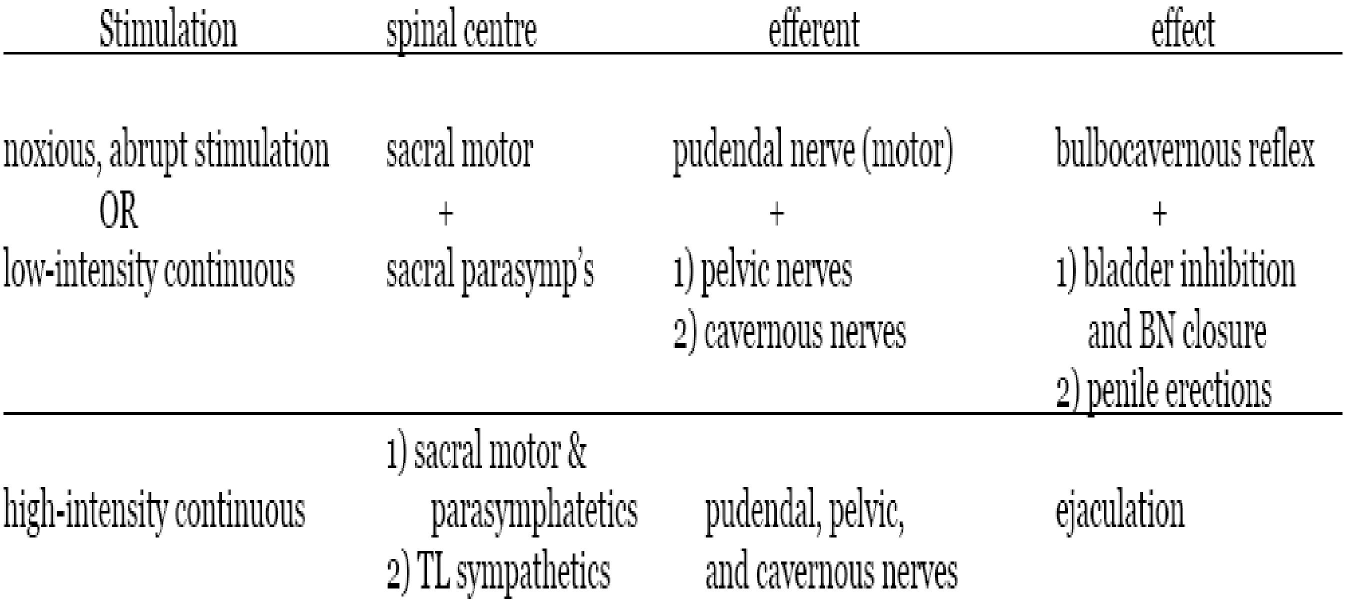
1) transient intracorporeal pressure increase } start of smooth muscle contraction
2) slow pressure ↓ } slow reopening of venous channels + resumption of basal level of arterial flow
3) fast pressure ↓ } fully restored venous outflow capacity

the hemodynamics of the corpus spongiosum differ from the corpora cavernosa

- pressure is only 1/3 to 1/2 that in the corpora cavernosa
  → thinner tunica albuginea over spongiosum and virtually absent over the glans
- contraction of ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, resulting in increased pressure of spongiosum + glans

Neuroanatomy and neurophysiology overview

spinal reflexes are elicited with stimulation of penile dorsal nerve (somatic + ?parasympathetic) is



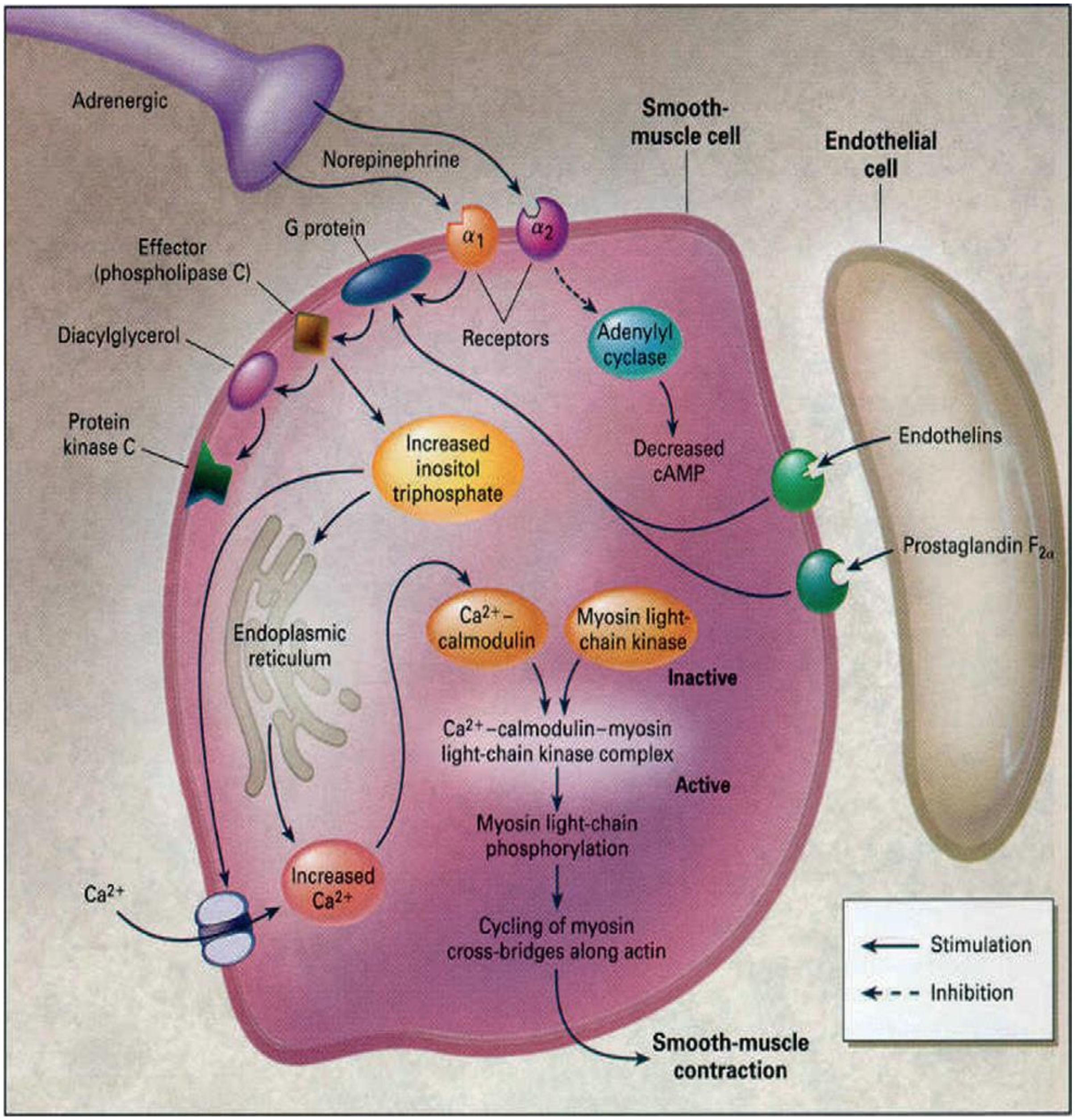
Stimulation	spinal centre	efferent	effect
noxious, abrupt stimulation OR low-intensity continuous	sacral motor + sacral parasymp's	pudendal nerve (motor) + 1) pelvic nerves 2) cavernous nerves	bulbocavernous reflex + 1) bladder inhibition and BN closure 2) penile erections
high-intensity continuous	1) sacral motor & parasymphatetics 2) TL sympathetics	pudendal, pelvic, and cavernous nerves	ejaculation

Which supraspinal brain centres are involved in sexual function (CHART)?

Level	Region	Function
forebrain	- medial amygdala	- controls sex drive
	- stria terminalis	
	- pyriform cortex	- inhibits sex drive
	- **hippocampus**	- erections
	- R insula + inferior frontal cortex	- sexual arousal
	- L anterior cingulate cortex	
hypothalamus	- **medial preoptic area (MPOA)**	- recognition of sexual partner
	- **paraventricular nucleus (PVN)**	- erections
brain stem	- nucleus paragigantocellularis	- inhibits erections
	- A5-catecholaminergic cell group	- innervates perineal muscles
	- locus ceruleus	
midbrain	- periaqueductal gray	- relay centre for sexual stimuli

Mechanism of flaciddity

Norepinephrine from sympathetic nerve endings and endothelins and prostaglandin F2α from the endothelium activate receptors on smooth muscle cells to initiate the cascade of reactions that eventually result in elevation of intracellular calcium concentrations and smooth muscle contraction**.**



factors involved in maintenance of flaccidity

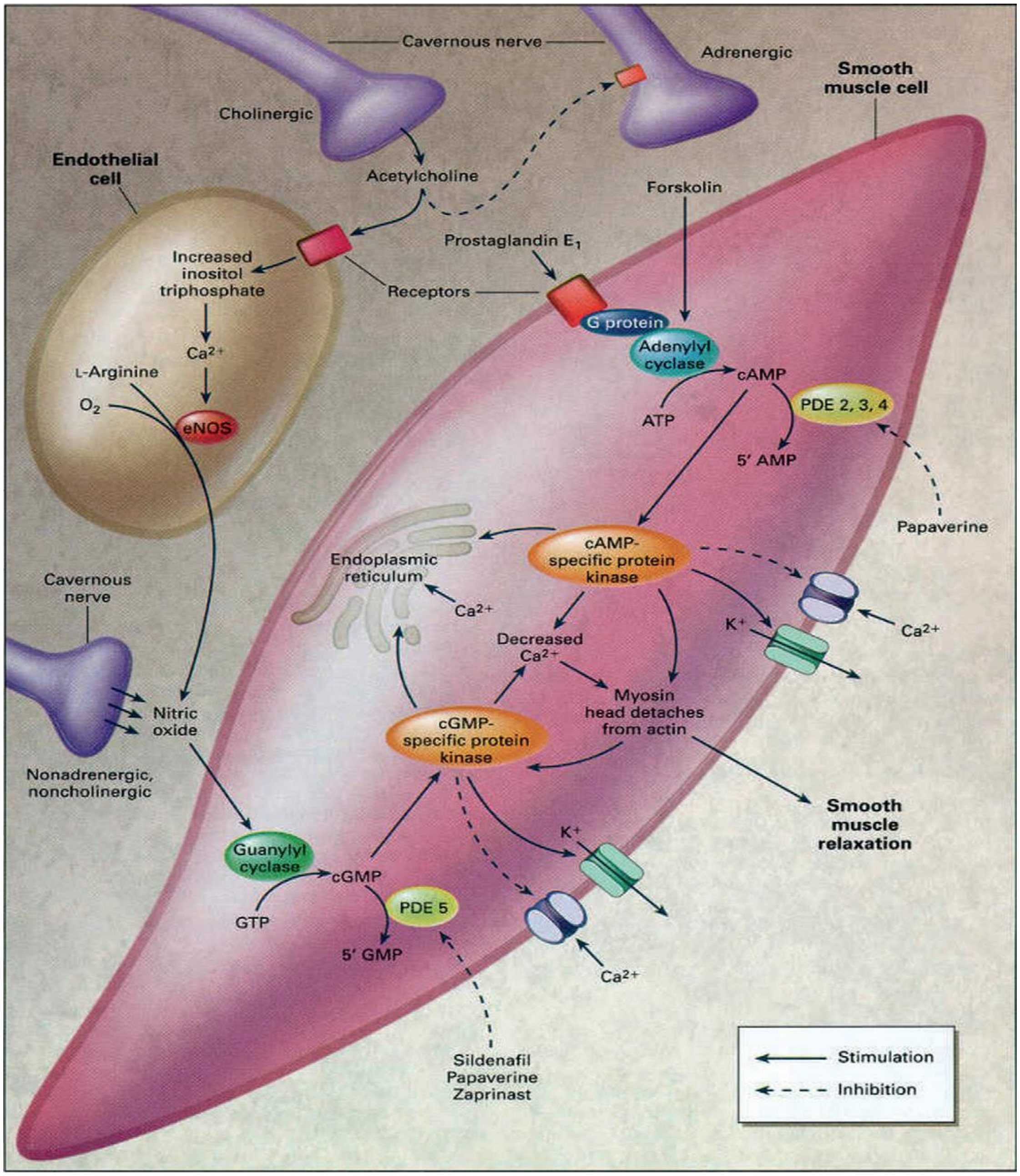
1) intrinsic myogenic activity of smooth muscles
2) adrenergic neurotransmitters
    - **NE** } **principle neurotransmitter**

      } α-adrenergic receptors >>> β-adrenergic receptors
3) endothelin-derived contracting factors } elevated intracellular Ca
    - **endothelin** } most potent vasoconstrictor

      } involves degradation of inositol phosphate (IP) & activation of protein kinase C
    - **prostaglandins (PGF2α)**
    - AT II
    - TXA2

Mechanism of erection

cAMP and cGMP, activate specific protein kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium leads to smooth muscle relaxation.



peripheral neurotransmitters are involved in erections

1) NO } principle neurotransmitter
    - □ from non-adrenergic, non-cholinergic (NANC) neurotransmission & from endothelium
    - □ **binds to guanalyl cyclase and ↑'s production of cGMP & cAMP**
        - cGMP and cAMP then activates protein kinases resulting in
        1) opening of K channels + hyperpolarization
        2) sequestration of intracellular Ca into ER
        3) blockage of Ca influx by inhibition of voltage-gated Ca channels
        - ↓'d levels of intracellular Ca results in smooth muscle relaxation

    Factors increase or decrease NOS levels

    - □ increase
        - oxygen
        - androgens
        - L-arginine
        - PGE1
    - □ decrease
        - castration
        - denervation
        - DM
        - increased cholesterol

2) acetylcholine } minor role
3) PGs } **PGE1 is pro-erectile via adenylyl cyclase**
4) VIP

central neurotransmitters are involved in erections

□ +ve effects on erections/sex drive

1) dopamine } D1 and D2 receptors
2) NE
3) oxytocin
4) NO
5) melanocortins
6) serotonin (5-HT1)

□ - ve –ve effects on erections/sex drive

1) prolactin
2) opioids
3) GABA
4) serotonin (5-HT2, 5-HT3)

factors responsible for detumesons

1) cessation of NO release
2) breakdown of cGMP by PDE
3) sympathetic upregulation with ejaculation

phosphodiesterase (PDE)

- enzyme that catalyzes the hydrolysis of cGMP and cAMP
- consists of 11 subtypes
  - all have been found in corpus cavernosum **EXCEPT PDE6** **(photoreceptor cells)** SO side effect of Viagra (blue hue)
  - **PDE5 is the main phosphodiesterase in the penis responsible for breakdown of cGMP**
  - PDE11 found in skeletal muscle SO □ side effect of cialis (back pain)
- **papaverine** inhibits **PDE2, PDE3, PDE4, PDE5**

Types of erection

1) psychogenic } from audiovisual stimuli or fantasies

} brain modulates spinal erection centres (T11-L2 and S2-S4)

2) reflexogenic } from tactile stimulation of genitals (S2-S4)

} some sensory info to brain but also direct autonomic activation of cavernous nerves for erections

3) nocturnal } occurs during REM and associated with testosterone levels

Effect of spinal cord injury on erection

 cerebral impulses travel via sympathetics (T11-L2)

 depends on location & nature of injury

 can also impair ejaculation and orgasm

 complete above T9 **upper cord } YES reflexogenic erections but NO psychogenic erections**

 complete sacal lower cord } NO reflexogenic erections (rare) but YES psychogenic erections

Effects of aging on erectile function

 likely an effect on endothelial NO (important in maintaining erections)

- greater latency to erection
- less turgidity
- loss of forceful ejaculation
- decreased ejaculate volume
- longer refractory period
- decreased frequency and duration of nocturnal erections

ERECTILE DYSFUNCTION

Definition

persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance.

it affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners.

Epidemiology

The incidence increase with age

- □ <10% of men <40yrs,
- 10-30% for men 40-60yrs,
- 20-40% for men 60-70yrs
- 40-70% for men >70yrs

Risk factors

Erectile dysfunction shares common risk factors with cardiovascular disease so Men complaining of mild ED should be evaluated adequately (for underlying cardiovascular risk

- lack of exercise,
- obesity,
- smoking,
- hypercholesterolaemia,
- DM
- poor general health status
- cardiovascular RFs (CAD, HTN, PVD)

causes of ED

1- ORGANIC
2- PSYCHOGENIC

psychogenic causes are

A. generalized classified into
   } unresponsiveness
   - primary lack of sexual arousability
   - aging-related decline in sexual arousability

   } inhibition

   - chronic disorder of sexual intimacy

B. situational classified into
   } partner-related
   - lack of arousability in specific relationship
   - lack of arousability owing to sexual object preference
   - high central inhibition owing to partner conflict or threat

   } performance-related

   - associated with other sexual dysfunction (eg rapid ejaculation)
   - situational performance anxiety (eg fear of failure)

   } psychological distress- or adjustment-related

   - associated with negative mood state (eg depression) or major life stress (eg death of partner)

mechanisms of psychogenic ED are

1) direct inhibition of spinal erection centre by brain
      exaggeration of N suprasacral inhibition
2) excessive sympathetic outflow or elevated peripheral catecholamine levels
      increase in penile smooth muscle tone to prevent relaxation

Organic causes are

A. vasculogenic
    arteriogenic (arterial, arteriolar)
    cavernosal (tunica albuginea, cavernous smooth muscle, endothelium, emissary vein, gap junction, fibroelastic trabeculae)
    mixed
B. neurogenic central, spinal, peripheral
C. anatomic
D. endocrinologic (testicular, pituitary, thyroid)
E. drug induced

***** most cases of ED are mixed etiology *****

A. vasclugenic

mechanisms of vasculogenic ED

1) structural changes
- decreased oxygen tension } less smooth muscle content + diffuse venous leakage
2) vasoconstriction
- increased basal tone + enhanced sympathetic activity + vascular wall hypertrophy
3) impaired endothelium-dependent vasodilation
- decreases acetylcholine-induced vasorelaxation

venogenic causes ED (veno-occlusive dysfunction)

1) degenerative tunical changes \ Peyronie's, DM, old age
2) fibroelastic structural alterations / penile fracture, etc
3) insufficient trabecular smooth muscle relaxation } excessive adrenergic tone, decreased NO
4) venous shunts } trauma, iatrogenic

B. Neurogenic

central

- Parkinson’s disease
- stroke
- encephalitis
- temporal lobe epilepsy
- tumours
- dementia +/- alzheimer’s
- Shy-Drager syndrome
- trauma

spinal

- trauma
- syringomyelia
- tumour
- spina bifida
- transverse myelitis
- MS

peripheral

- iatrogenic post RP
- trauma
- peripheral
- neuropathy

C. anatomic

- Peyronie’s disease
- Penile fracture
- Congenital curvature of the penis
- Micropenis
- Hypospadias, epispadias

D. endocrinologic (testicular, pituitary, thyroid)

- Hypogonadism
- Hyperprolactinemia
- Hyper- and hypo-thyroidism
- Cushing's disease

E. drug induced

- 1) **A**nti-hypertensives } diuretics
} non-selective β-blockers (eg propranolol, guanethidine)
□ α **1-blockers and ARBs actually improve erectile function**
□ **ACEI and CCB have no effect**

2) α -agonists } clonidine, methyldopa

3) **A**nti-psychotics } resperidone, clozapine
□ decreased dopamine (increases prolactin), β-blockade
□ older "typicals" worse for EPS

4) **A**nti-depressants } TCA (peripheral anticholinergic + β-adrenergic effects)
} MAO inhibitors (orgasmic dysfunction by unclear mechanism)
} SSRIs eg paroxetine (increased serotonin 5-HT2, 5-HT3, decreased dopamine)

5) **A**nxiolytics } benzo's (upregulate GABA, decreased dopamine)
□ trazodone (priapism risk) works by up-regulating 5-HT1 (pro-erectile)

6) **A**nti-androgens } 5ARIs, nonsteroidal anti-androgens (flutamide, bicalutamide), steroidal anti-androgens (cyproterone), LHRH agonists

7) **A**lcohol abuse + tobacco

8) **C**hemo, **H**2-blockers (cimetidine), **O**piates, **P**rotease inhibitors, **D**igoxin, etc

Diagnostic evaluation

A. History taking

i. Detailed sexological history, it must include
  - information about previous and current sexual relationships,
  - onset and duration of the erectile problem,
  - previous consultations and treatments.
  - A detailed description of the rigidity and duration of both sexually stimulated and morning erections and of problems with arousal, ejaculation, and orgasm.
  - psychometric questionnaires, such as the International Index for Erectile Function (IIEF)
  - Psychometric analysis of erectile hardness score.

ii. Detailed medical history atherosclerosis, CAD, PVD, HTN, cholesterol, DM, anxiety, depression, psych hx, pelvic/perineal surgery or trauma, Peyronie’s, priapism, neurologic disease

iii. psychosocial hx } past & present partner relationships, job status, family situation AND use of a 2-question scale for depression: “During the past month

iv. meds (old & new), allergies, EtOH, smoking, recreational drugs

v. Patients should be screened for symptomatic lower urinary tract symptoms.
 assess for contraindications to drug therapy

B. Physical examination

It should focused on the genitourinary, endocrine, vascular, and neurological systems.

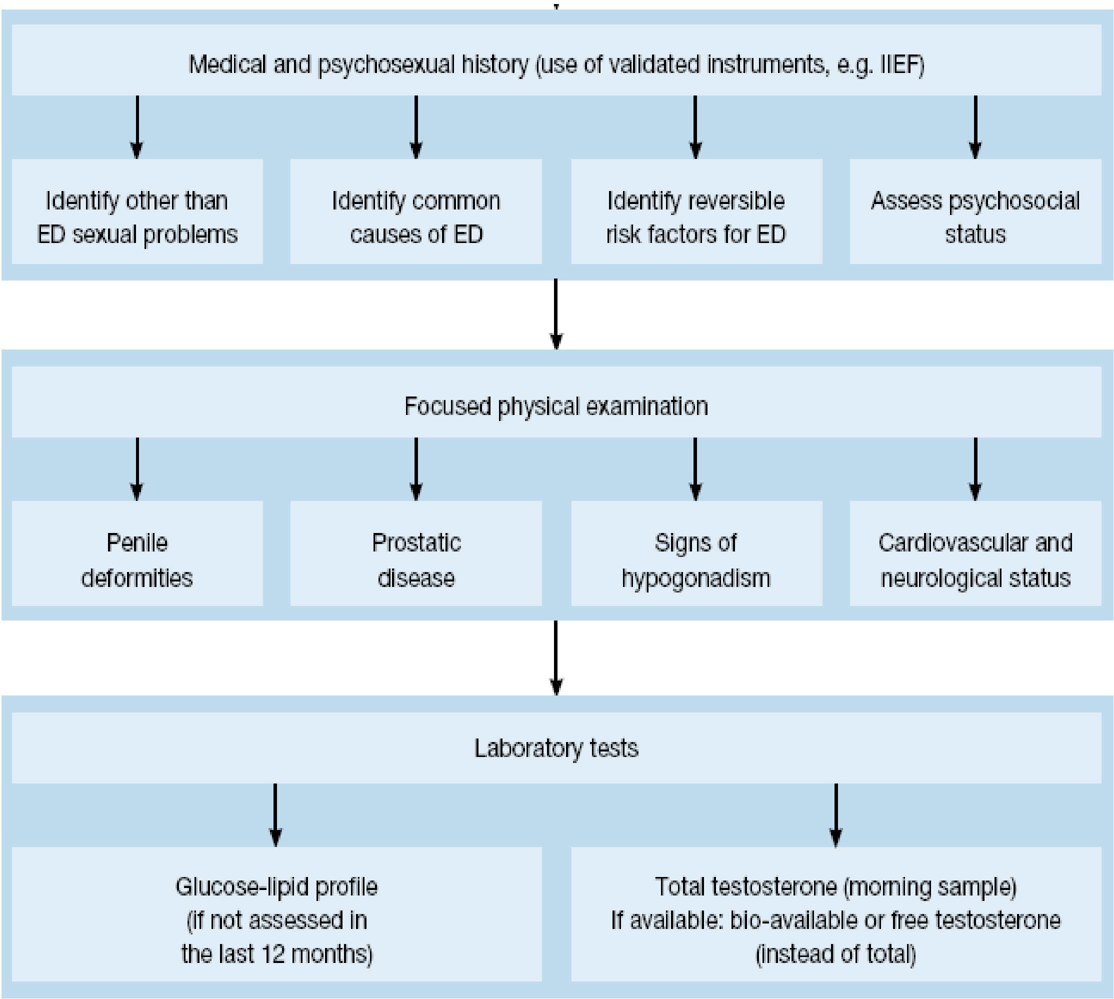
- general appearance (body habitus), vitals (BP) secondary sexual characteristics, gynecomastia
- abdo exam } masses, palpable bladder, CVA tenderness
- **peripheral vascular exam** Blood pressure and heart rate should be measured
- cardiac exam
- neuro exam } peripheral, spinal, supraspinal (somatic, autonomic)
- genital exam } phallus size, chordee, Peyronie’s plaque, testis size, DRE, rectal tone

C. Laboratory testing

- a fasting glucose or HbA1c
- lipid profile.
- PSA
- hormonal tests
  - ✚ a morning sample of total testosterone. or calculated-free testosterone
  - ✚ prolactin and luteinizing hormone, are performed when low testosterone levels are detected.

hormonal evaluation of a complex ED patient

- total/free/bioavailable testosterone
- SHBG (add albumin if severe liver disease)
- LH
- FSH
- prolactin
- TSH/T4
- adrenal failure


Medical and psychosexual history (use of validated instruments, e.g. IIEF)
Identify other than ED sexual problems
Identify common causes of ED
Identify reversible risk factors for ED
Assess psychosocial status
Focused physical examination
Penile deformities
Prostatic disease
Signs of hypogonadism
Cardiovascular and neurological status
Laboratory tests
Glucose-lipid profile (if not assessed in the last 12 months)
Total testosterone (morning sample)
If available: bio-available or free testosterone (instead of total)

Minimal diagnostic evaluation (basic work-up) in patients with ED

D. Specialised diagnostic tests

Indications

- Primary erectile disorder (not caused by organic disease or psychogenic disorder)
- Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery
- Patients with penile deformities that might require surgical correction, e.g. Peyronie’s disease, congenital curvature
- Patients with complex psychiatric or psychosexual disorders
- Patients with complex endocrine disorders
- at the request of the patient or his partner
- Medicolegal reasons, e.g. implantation of penile prosthesis, sexual abuse

Specific diagnostic tests

1- Nocturnal penile tumescence and rigidity (NTPR) using Rigiscan®
2- Vascular studies

   1st line
      - Combined Intracavernous injection test (ICI) + Stimulation testing (CIS)

   ☐ 2nd line
      - ICI + color Doppler U/S

   ☐ 3rd line
      - dynamic infusion cavernosometry and cavernosography (DICC)
      - arteriography

3- Neurological studies, e.g. bulbocavernosus reflex latency, nerve conduction studies
4- Endocrinological studies
5- Specialised psychodiagnostic evaluation

1- Nocturnal penile tumescence and rigidity (NTPR) using Rigiscan®

It differentiate between psychogenic and organic ED

loop placed on base of penis and at coronal sulcus .It should be done on at least two nights.

A functional erectile mechanism is indicated by

- an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for > 10 min.
- increased tumescence of circumference >3cm at base and >2cm at tip
- >4-5 erections per night (80% occur during REM)

2- Intracavernous injection test

A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min.

A positive test shows that a patient will respond to the intracavernous injection programme.

N CIS = N venous occlusion

Disadvantages

- This response indicates a functional, but not necessarily normal, erection, as erection may coexist with arterial insufficiency and/or veno-occlusive dysfunction
- The test is inconclusive as a diagnostic procedure and duplex Doppler study of the penis should be requested, if clinically warranted.

3- Duplex ultrasound of the penis

often performed after ICI (alprostadil 20-60□g) + stimulation

normal parameter is

- A peak systolic blood flow > 30 cm/s,
- an end-diastolic velocity of < 3 cm/s
- a resistance index > 0.8 are normal
- arterial dilation after ICI is >75% (N is >1.5mm) .

Advantages

- excellent vasculogenic information
  PSV >25cm/sec + EDV >5cm/sec + early detumescence after ICI = veno-occlusive dysfxn
  Resistive index at 20 mins <0.75 = venous leakage
- good for high-flow priapism and localization of a ruptured artery
- Further vascular investigation is unnecessary when a Duplex examination is normal.

4- and dynamic infusion cavernosometry or cavernosography(DICC)

Indication : in patients who are being considered for vascular reconstructive surgery.

1) hx of pelvic trauma

2) hx of primary ED

Methods : (2 needles in penis for NS infusion + pressure recording) , must have complete smooth muscle relaxation (need multiple injections of vasoactive agent)

interpretation: flow rate req’d to maintain erection at >100 mmHg = <5ml/min

5- Arteriography

assess internal iliac, internal pudendal, and penile arteries also assess inferior epigastrics most commonly used for penile revascularization sx

indication

 mainly to get anatomic info to plan surgical reconstruction
1) young male with ED secondary to traumatic arterial disruption
2) hx of perineal compression injury

6- Psychiatric assessment

Indication

- Patients with psychiatric disorders
- younger patients (< 40 years) with long-term primary ED

7- neurological assessment

1) somatic

- biothesiometry: measure sensory perception thresholds to vibratory stimulation
- sacral evoked response-BCR latency: abN if >3 standard deviations above mean of 30-40 ms
- dorsal nerve conduction velocity : avg is ~25 m/sec
- genito-cerebral evoked potential

2) autonomic

- heart rate variability and sympathetic skin response
- penile thermal sensory testing
- corpus cavernosum EMG

Cardiovascular system and sexual activity:

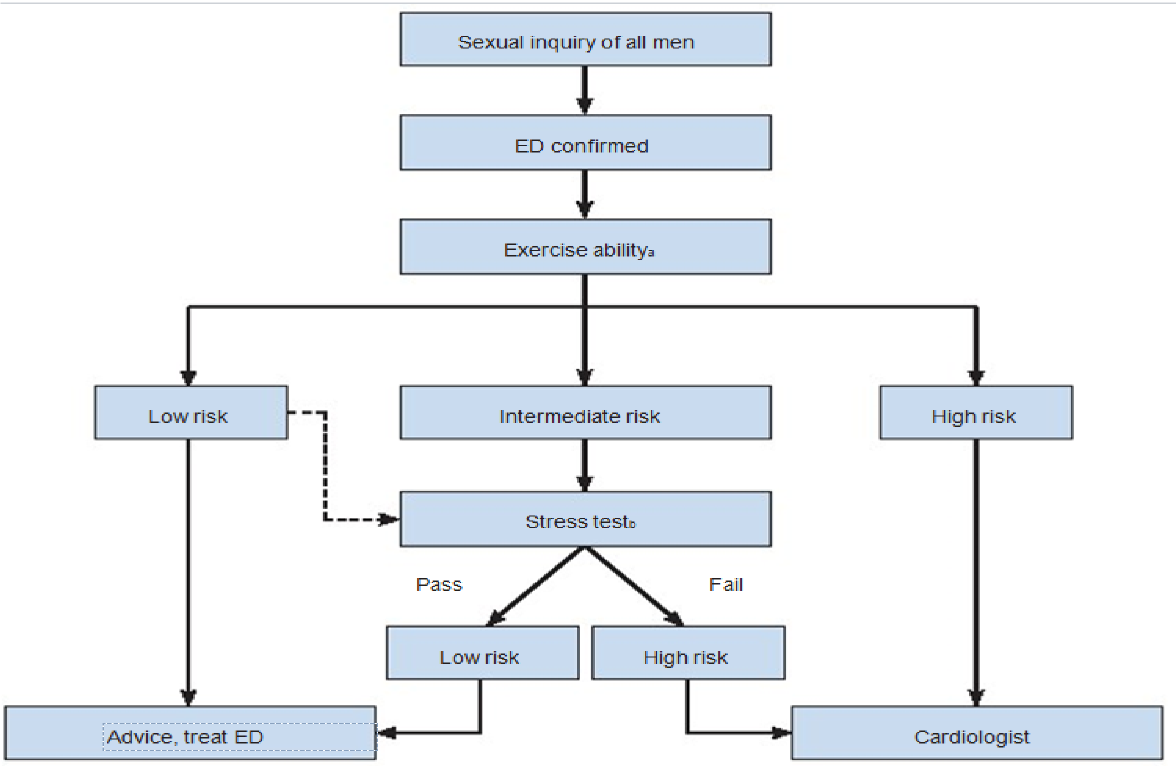
There is an association between coronary heart disease, stroke and sexual dysfunction. So patients who seek treatment for sexual dysfunction have a high prevalence of cardiovascular disease.

Patients with ED can be stratified into three cardiovascular risk categories from their level of exercise tolerance. which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity

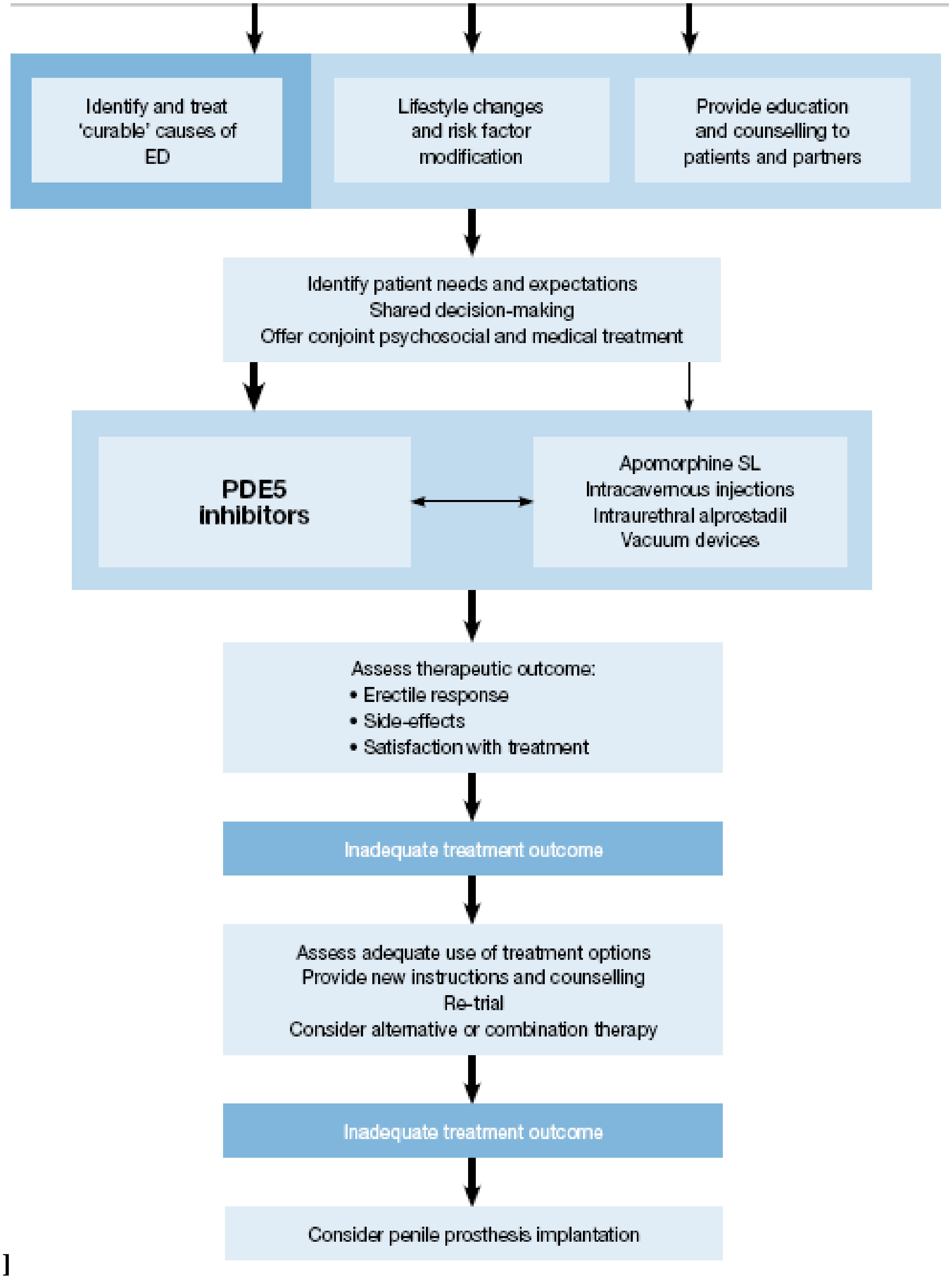
Table 2: Cardiac risk stratification

Low-risk category	**Intermediate-risk category**	**High-risk category**
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.



TREATMENT OF ERECTILE DYSFUNCTION


Identify and treat 'curable' causes of ED
Lifestyle changes and risk factor modification
Provide education and counselling to patients and partners
Identify patient needs and expectations
Shared decision-making
Offer conjoint psychosocial and medical treatment
PDE5 inhibitors
Apomorphine SL
Intracavernous injections
Intraurethral alprostadil
Vacuum devices
Assess therapeutic outcome:
• Erectile response
• Side-effects
• Satisfaction with treatment
Inadequate treatment outcome
Assess adequate use of treatment options
Provide new instructions and counselling
Re-trial
Consider alternative or combination therapy
Inadequate treatment outcome
Consider penile prosthesis implantation

]

Specific

1- Lifestyle management

Lifestyle changes and risk factor modification eg wt loss, exercise, stop smoking, stop long-distance cycling must precede or accompany any pharmacological treatment.

A significant improvement can be expected as soon as after 3 months of initiating lifestyle changes

2- Treatment of curable causes

1- Hormonal causes

Referral to endocrinologist for managing patients with hormonal abnormalities.

2- Post-traumatic arteriogenic ED in young patients

surgical penile revascularisation.

Corporeal veno-occlusive dysfunction is is no longer recommended to revascularization and must be excluded by DICC because of poor long-term results

3- Psychogenic causes

psychosexual therapy either alone or with another therapeutic approach.

Non specific management

First-line therapy

A. Oral pharmacotherapy

Mechanism of action

PDE5 hydrolyses cGMP in the cavernosum tissue. Inhibition of PDE5 results in increase cGMP which lead to smooth muscle relaxation with increased arterial blood flow, leading to compression of the subtunical venous plexus and penile erection.

Types

I. Sildenafil (Viagra)

- It was the first PDE5I available on the market.
- It is effective from 30-60 min after administration and is maintained for up to 12 h
- Its efficacy is reduced after a heavy, fatty meal due to prolonged absorption.
- Doses : 25, 50 and 100 mg. The recommended starting dose is 50 mg .
- Adverse events are generally mild in nature and self-limited by continuous use.
- blue-hue vision cross-reactivity with PDE-6

II. Tadalafil (Cialis)

- It is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h
- It is not affected by food.
- Does 10 and 20 mg. The recommended starting dose is 10 mg
- Adverse events are generally mild in nature and self-limited by continuous use.
- lower back muscle pain } cross-reactivity with PDE-11

III. Vardenafil (Levitra)

- It is effective from 30 min after administration.
- Its effect is reduced by a heavy, fatty meal
- Does 5, 10 and 20 mg The recommended starting dose is 10 mg
- Adverse events are generally mild in nature and self-limited by continuous use
- blue-hue vision possible but much less common } cross-reactivity with PDE-6
- In vitro, it is 10-fold more potent than sildenafil, although this does not necessarily mean greater clinical efficacy
- only PDE5I with cardiac conduction precaution (QT prolongation)

Recently, a new formulation of vardenafil has been released, in the form of an orodispersable tablet (ODT). In compared to film coated

- It offer improved convenience so be preferred by patients. Absorption is unrelated to food intake
- It exhibit better bioavailability
- The efficacy did not seem to differ

Choice or preference between the different PDE5 inhibitors

- There is no available data
- Choice of drug will depend on the frequency of intercourse and the patient's personal experience.

side effects of PDE-5 inhibitors

- headache (most common)
- flushing
- slight lowering of BP
- dyspepsia
- rhinitis
- priapism
- nonarteritic anterior ischemic optic neuropathy

On-demand or chronic use of PDE5 inhibitors

chronic use of PDE5Is improves the intracavernous structure alterations

tadalafil

- does of chronic use 2.5 to 5 mg/day according to tolerability

vardenafil

- Does of chronic use 10 mg /day

Cardiovascular safety for PDE5 inhibitors

There is no increase in myocardial infarction rates in patients receiving PDE5Is

PDE5Is had no adverse effect on cardiac contractility, cardiac output or myocardial oxygen consumption .

Chronic or on-demand use is well tolerated with a similar safety profile.

Drug interaction with PDE5 inhibitors

1- Nitrates

- nitrates are absolute contraindications for the use of PDE5Is. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension.
- If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) is used (half-life, 4 h), and for at least 48 h if tadalafil is used (half- life, 17.5 h).
- If a patient develops angina while taking a PDE5I, other agents may be given instead of nitroglycerine . If nitroglycerine must be reintroduced , the patient should receive it only after an appropriate interval has elapsed, and under close medical observation.

2- Antihypertensive drugs

- Co-administration of PDE5Is with antihypertensive agents may result in small additive decreases in blood pressure, which are usually minor.

3- Alpha-blocker

All PDE5Is show some interaction with Alpha-blocker which may result in orthostatic hypotension.

- 50 , 100 mg of sildenafil should not be taken within 4 h following treatment with an alpha-blocker. This restriction does not apply to 25 mg dose of sildenafil.
- vardenafil and Tadalafil is absolutely contraindicated with alpha-blockers , except tamsulosin as it is not associated with clinically significant hypotensio.

Dosage adjustment

- lower doses of PDE5Is
  1) use of alpha-blockers (except flomax)
  2) liver failure
  3) renal failure
  4) 65 yrs old (start at 25mg)
  5) meds that block CYP3A4 pathway which will inhibit the breakdown of PDE5Is (ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (ritonavir and saquinavir, cipro , cyclosporine, CCB (verapamil)),

- rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required.

Management of non-responders to PDE5 inhibitors

Causes: incorrect drug use or lack of efficacy of the drug.

The management of non-responders.

a) Check that the patient has been using a licensed medication
b) Check that the medication has been properly prescribed and correctly used this is may be due to :

- Failure to use an adequate dose
- Failure to wait an adequate time between taking the medication and sexual intercourse.
- Ingestion of meal with the drug
- Failure to use adequate sexual stimulation: as PDE5Is depend for their action upon the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation and without adequate sexual stimulation (and NO release), the drugs cannot work.

Possible manoeuvres in patients correctly using a PDE5 inhibitor To improve druy efficacy in patient taking correct does

- normalisation of serum testosterone in hypogonadism patient
- Modification of other risk factors as DM , HTN
- switching PDE5Is.
- Use regular dosing with either vardenafil or tadalafil,
- If drug treatment fails, then patients should be offered an alternative therapy such as intracavernosal injection therapy or use of a vacuum erection device.

contraindications to PDE-5 inhibitor

 ABSOLUTE

- use of nitrates

 RELATIVE

- severe CV disease
- LV outflow obstruction
- MI within last 90 days
- unstable angina or angina during sex
- NYHA class ≥2
- uncontrolled arrhythmias, hypoTN, or uncontrolled HTN
- stroke within last 6 months
- hereditary retinal disorder (eg retinitis pigmentosa)
- high risk of priapism (sickle cell anemia, leukemia, etc)

B. Apomorphine sublingual

Mechanism of action

- It is a centrally acting dopamine agonist
- it improves erectile function by enhancing the natural central erectile signals

Dose :

- 2 or 3 mg sublingually on demand
- Due to rapid absorption, 71% of erections are achieved within 20 min

Adverse events

- nausea
- headache
- dizziness
- syncope, are extremely rare (< 0.2%)

Advantages

- It is a safe drug
- It is not contraindicated in patients taking nitrates or antihypertensive drugs
- it does not affect vital signs.

Disadvantages

- It is significantly lower efficacy rate than sildenafil .
- Efficacy rate range from 28.5% to 55%

Indication

- In patent with mild-to-moderate ED or psychogenic causes of sexual dysfunction due to reduced efficacy rates.
- In patients with certain contraindications for the use of PDE5 inhibitors, e.g. nitrates.

C. Vacuum erection devices (VEDs)

Mechanism of action

- provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. they do not use physiological erection pathways.

Indication

- well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED

Advantages :Highly efficacy, up to 90%, regardless of the cause of ED

contraindicated

- patients with bleeding disorders
- patient on anticoagulant therapy.

adverse events

- pain,
- inability to ejaculate,
- petechiae, bruising,
- numbness
- skin necrosis. It can be avoided if patients remove the constriction ring within 30 min.

D. Shockwave therapy

Effect of the use of low-intensity extracorporeal shock wave therapy

- It had a positive short-term clinical and physiological effect on the erectile function of men who respond to oral PDE5Is
- There is improvement in penile hemodynamics and endothelial function,
- There is improvement in IIEF-EF domain score in severe ED patients who are poor responders to PDE5Is

mechanism of action

unclear some reported that It promoting regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis. These effects is mediated by recruitment of endogenous mesechymal stem cells (MSCs)

E. Other oral agents

To day there is no place for these drugs in the treatment of ED.

- Yohimbine is a centrally and peripherally active alpha-2 adrenergic antagonist used as an aphrodisiac for almost a century.
- Delequamine is a more specific and selective alpha-2 adrenergic antagonist than yohimbine.
- Trazodone is a serotonin reuptake inhibitor (antidepressant) associated with prolonged erections and priapism. It is also a non-selective alpha-adrenergic antagonist in the corporal smooth muscle cells.
- L-arginine is a nitric oxide donor and nalmefene/naltrexone is an opioid-receptor antagonist.
- Red Korea ginseng is a formulation with an unknown mechanism of action (though it may possibly act as a nitric oxide donor).
- Limaprost is an alprostadil derivative for oral use.
- An oral formulation of phentolamine (non-selective alpha-adrenergic antagonist)

F. Topical pharmacotherapy

these agents have no role in treatment of ED.

Several vasoactive drugs (2% nitroglycerine, 15-20% papaverine gel, and 2% minoxidil solution or gel) have been used for topical application to the penis.

To overcome the poor drug absorption through the thick and dense tunica albuginea, several drug absorption enhancers have been developed for combination with vasoactive drugs.

Adverse events include skin and glans erythema, burning sensation, allergic reactions, and side-effects in the partner (hypotension, headache) due to vaginal absorption.

Second-line therapy

A. Intracavernous injections

Indication Patients not responding to oral drugs

Advantages Success rate is high (85%)

contraindications

☐ ABSOLUTE

1) sickle cell anemia
2) schizophrenia or severe psych disorder
3) severe systemic disease (unstable CAD)
4) penile prosthesis

☐ RELATIVE

1) use of anticoagulant or ASA compression x 5-10 min

complication

- priapism
- fibrosis
- hematoma
- pain
- nodules and plaques
- urethral injury

1. **Monotherapy Alprostadil** (CaverjectTM, Edex/ViridalTM)

It was the first and only drug approved for intracavernous treatment

dose of 5-40 μg;

The erection appears after 5-15 min and lasts according to the dose injected.

The use of an automatic special pen avoids a view of the needle can resolve fear of penile puncture and simplifies the technique.

Complications

- penile pain (50%) Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia
- prolonged erections (5%),
- priapism (1%),
- Cavernosal fibrosis (2%) (from a small hematoma)
- Systemic side effects are uncommon. The most common is mild hypotension, especially when using higher doses.

Contraindications

- hypersensitivity to alprostadil,
- men at risk of priapism,
- men with bleeding disorders.

Discontinuation of treatment

- it occur within the first 2-3 months
- it occur in 27%
- it may be due to
  - desire for a permanent modality of therapy,
  - lack of a suitable partner ,
  - poor response ,
  - fear of needles
  - fear of complications
  - lack of spontaneity

2. Combination therapy

Advantages

- enables a patient to take different modes of action
- alleviating side-effects by using lower doses of each drug.

Most combinations are not standardised .

- Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg)
- papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 μg),
  - it is the widely used combination
  - it improved efficacy rates up to 92%
  - this combination had similar side-effects as alprostadil monotherapy,
  - it has a lower incidence of penile pain due to lower doses of alprostadil.
  - fibrosis was more common (5-10%) when papaverine was used (depending on total dose)
- The combination of sildenafil with intracavernous injection of the triple combination regimen in patients do not respond to combination intracavernous injections alone .

3. Intraurethral alprostadil

indication it is an alternative to intracavernous injections in patients who prefer a less-invasive,

alprostadil (125-1000 µg) in medicated pellet (MUSETM)

low success rate 30-65.9% .this rate can increase by application of a constriction ring at the root of the penis

adverse events

- local pain (29-41%)
- dizziness with possible hypotension (1.9-14%).
- Penile fibrosis and priapism are very rare (< 1%).
- Urethral bleeding (5%)
- urinary tract infections (0.2%) .

Third-line therapy (penile prostheses)

Indication

- patients who do not respond to pharmacotherapy
- who prefer a permanent solution to their problem.

Types

- malleable devices .
- inflatable (2- and 3-piece)

The three-piece inflatable devices

- it is the prefer one in most patient due to the natural erections obtained.
- The third piece is a separate reservoir placed in the abdominal cavity.
- It provide the best rigidity and the best flaccidity .

The two-piece inflatable prosthesis

- it can be a viable option among patients who are deemed high risk of complications with reservoir placements.

Malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state.

Surgical approaches for penile prosthesis implantation

A. peno-scrotal

advantages

- it provides an excellent exposure,
- it affords proximal crural exposure if necessary,
- avoids dorsal nerve injury
- permits direct visualisation of pump placement.

Disadvantages ,

- the reservoir is blindly placed into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy).

B. infrapubic

advantage

- eservoir placement under direct vision

disadvantages

- the implantation of the pump may be more difficult ,
- increased risk of dorsal nerve injury.
- Revision surgery is associated with decreased outcomes and may be more difficult .

Efficacy and satisfaction rates

highest satisfaction rates (92-100% in patients and 91-95% in partners)

at 3 months following surgery, the results were less satisfactory There was a continued improvement in scores for stabilised 1 year following surgery.

the presence of urinary incontinence and sexual dysfunction after RP is leading doctors to the need for management of both conditions. combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established, definitive role to address this problem.

Erectile dysfunction after radical prostatectomy

Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED

25-75% of men experience ED post radical prostatectomy

Etiology of post-RP ED

- Cavernosal nerve injury
- arterial damage which lead to poor oxygenation

both can induces proapoptotic (loss of smooth muscle) and profibrotic (increase in collagen) factors within the corpora cavernosa.

Factor affects postoperative ED

- Experience of the surgeon "most important"
- Preoperative potency "most important"
- preservation of neurovascular bundles
- patient age.
- the role of vascular insufficiency is of increasing interest in (30,31).

The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue cryotherapy and high-intensity focused ultrasound for prostate cancer are associated with equivalent or worsened rates of ED compared to surgery or radiation therapy

Treatment

Early compared with delayed erectile rehabilitation brings forward the natural healing time of potency so use of proerectile drugs following RP is advice.

There is higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED.

Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa .

Daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery.

Patients who do not respond to oral PDE5Is may be treated with prophylactic intracorporeal alprostadil

Penile prosthesis remains a satisfactory approach for patients who do not respond to either oral or intracavernous pharmacotherapy or to a vacuum device (29).

COLLECTIONS

commonly referenced questionnaires used to assess sexual function

1) IIEF } International Index of Erectile Function
2) SHIM } Sexual Health Inventory for Men
3) BMSFI } Brief Male Sexual Function Inventory
   ☐ sex drive (2 items), erections (3 items), ejaculation (2 items), perception of problems (3 items), overall satisfaction (1 item)

IIEF-15

- most widely used & statistically validated in many languages
- 15 items total with 5 domains:
  1) **sexual desire**
  2) **erectile function**
  3) **intercourse satisfaction**
  4) **orgasmic function**
  5) **overall satisfaction**
- total score **out of 75** (minimum is 5)

☐ measures over the **past 4 weeks**

IIEF-5

- shorter 5 item version of IIEF-15 looking mainly at erectile function
- 4 items from erectile function domain + 1 item from sexual intercourse satisfaction domain
- total score out of 25 (minimum is 5) } 22 to 25 = no ED
  } 17 to 21 = mild ED
  } 12 to 16 = mild to moderate ED
  } 8 to 11 = moderate ED
  } 5 to 7 = severe ED

☐ IIEF-5 measures **over past 6 months**

features on history suggest a psychogenic cause of ED

- acute onset
- situational ED
- variable course
- rigid non-coital erections
- long history of psychosexual problems
- primary anxiety and fear

1ry ED

□ lifelong inability to initiate or maintain erections

1) **psychogenic (majority)**
2) organic } less common
    } congenital malformation leading to neurologic, arterial, & veno-occlusive dysfxn
    } endocrine cause uncommon (low sex drive is usually main symptom)
        □ can lead to micropenis, hypospadias, epidspadias, etc

Papaverin

- alkaloid from opium
- **PDE2,3,4,5 inhibitor } increases cGMP & cAMP**
- **also CCB effect**
- metabolized in liver
- T1/2 = 1-2hrs

□ priapism and fibrosis, can raise LFTs

phentolamine

- competitive □□-blocker } □1 and □2 affinity
- T1/2 = 30 mins

□ hypoTN, reflex tachycardia, nasal congestion, GI upset alprostadil

- **PGE1**
- smooth muscle relaxant, vasodilator, platelet aggregation inhibitor } **increased cAMP**
- metabolized by PG-15-hydroxydehydrogenase (present in penis)
- T1/2 = 60 mins

□ painful erections (almost never see priapism)

Management of ED in renal failure

Medical

1) optimize general condition
a) atherosclerotic risk factors
b) ED-inducing drugs
c) adequate dialysis
2) Viagra – ↓ dose
a) renal dosing: start 25 mg od
b) cyclosporine: start 25 mg od

Surgical

1) transplant: returns 80% of pts to pre-failure potency
2) semi-rigid prosthesis:
   a) more reliable (↓ re-operation rate)
   b) no peri-vesical reservoir to get in way of transplant
   3) inflatable prosthesis
   a) use a scrotal reservoir

PREMATURE EJACULATION(PE)

There are 2 definition

1. Ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control.

2. It is a male sexual dysfunction characterised by ejaculation which always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy'.

It is important to distinguish PE from ED.as many patients with ED develop secondary PE. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE

Epidemiology

- It is the most common male sexual dysfunction, with prevalence rates of 20-30%
- lifelong PE, defined as IELT < 1-2 min, is about 2-5%
- PE is more common in blacks, Hispanic men and men from Islamic backgrounds and may be higher in men with a lower educational level

etiology and risk factors

the pathophysiology of PE is unknown.

It may be due to

- psychological hypotheses,
- anxiety
- penile hypersensitivity,
- 5-HT receptor dysfunction
- genetic predisposition
- poor overall health status and obesity
- prostate inflammation
- thyroid hormone disorders
- emotional problems and stress
- traumatic sexual experiences

Classifications

- ‘lifelong’ (primary) is characterised by
    - onset from the first sexual experience,
    - remains so during life
    - ejaculation occurs too fast (before vaginal penetration or < 1-2 min after).
- ‘acquired’ (secondary) is characterised by
    - a gradual or sudden onset following normal ejaculation experiences before onset
    - time to ejaculation is short (usually not as short as in lifelong PE).

Recently, two more PE syndromes have been proposed :

- ‘Natural variable PE’ is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- ‘Premature-like ejaculatory dysfunction’ is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer.

Diagnosis

History should classify PE as

- lifelong or acquired and determine
- situational (under specific circumstances or with a specific partner) or consistent.

Special attention should be given to

- the duration time of ejaculation
- degree of sexual stimulus,
- impact on sexual activity and QoL,
- drug use or abuse.
- **Intravaginal ejaculatory latency time**

  The use of IELT alone is not sufficient to define PE

  self-estimated IELT have to be combining with a single-item patient-reported outcome (PRO) on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all to 4 = extremely).

  stopwatch-measured IELT is necessary in clinical trials

- **PE assessment questionnaires**

2 questionnaires can discriminate between patients who have PE and those who do not:

1. Premature Ejaculation Diagnostic Tool (PEDT: five-item questionnaire. Assesses control, frequency, minimal stimulation, distress and interpersonal difficulty .
2. Arabic Index of Premature Ejaculation (AIPE): seven-item questionnaire. assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction for the patient and partner, anxiety or depression .

Physical examination and investigations

It includes a brief examination of the vascular, endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions.

Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended

Treatment

I. Psychological/behavioural strategies

1. ‘stop-start’ programme, in which the partner stimulates the penis until the patient feels the urge to ejaculate. At this point, he instructs his partner to stop, waits for the sensation to pass and then stimulation is resumed.
2. ‘squeeze’ technique is similar but the partner applies manual pressure to the glans just before ejaculation until the patient loses his urge.

Both these procedures are applied in a cycle of three pauses before proceeding to orgasm.

3. Masturbation before sexual intercourse as following masturbation, the penis is desensitised resulting in greater ejaculatory delay after the refractory period is over.
4. In a different approach, the man learns to recognise the signs of increased sexual arousal and how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex. .

Disadvantages

- success rates of 50-60%
- that improvements achieved with these techniques are generally not maintained long term
- pharmacological treatment resulted in greater IELT prolongation than behavioural therapy

II. Topical anaesthetic agents

It is the oldest form of pharmacological therapy

Mechanism of action topical desensitising agents reduce the sensitivity of the glans penis so delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

1. Lidocaine-prilocaine cream(5%)

It is applied for 20 to 30 min prior to intercourse.

Precaution

- Prolonged application of topical anaesthetic (30 to 45 min) may result in loss of erection due to numbness of the penis
- A condom is required to avoid diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner. Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound.
- It is contraindicated in patients or partners with an allergy to any component of the product.

2. SS-cream

It is applied to the glans penis 1 h before and washed off immediately prior to coitus.

It is a dose- dependent fashion

Does 0.2 g

Side effect

- Mild local burning and mild pain.
- No adverse effects on sexual function or partner
- No systemic side-effects

III. Selective serotonin reuptake inhibitors

Ejaculation is mediated by

- spinal ejaculation generator
- descending supraspinal modulation from several brain regions.
- The neurotransmitter is 5-hydroxytryptamine (5-HT, serotonin) .

The retarding effect of 5-HT on ejaculation is probably due to central activation (i.e. spinally and supraspinally) of 5-HT1B and 5-HT2C receptors, while stimulation of 5-HT1A receptors precipitates ejaculation.

Clomipramine 25-50 mg, serotoninergic tricyclic antidepressant, was first reported as an effective PE treatment

SSRIs has become the first choice of treatment in PE. Commonly used SSRIs include

- paroxetine 20-40 mg
- fluoxetine
- sertraline 25-200 mg
- fluvoxamine, 10-60 mg
- citalopram

precaution

- Ejaculation delay may start a few days after drug intake, but it is more evident after 1 to 2 weeks so SSRIs must be given for 1 to 2 weeks to be effective in PE
- tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6 to 12 months . this is due to chronic SSRI administration causes prolonged increases in synaptic cleft serotonin, which desensitise the 5-HT1A and 5-HT1B receptors.

side-effects they are usually mild and gradually improve after 2 to 3 weeks

- fatigue, drowsiness, yawning,
- nausea, vomiting,

- dry mouth,
- diarrhoea
- perspiration.
- Decreased libido,
- anorgasmia,
- anejaculation
- ED.

on-demand use of clomipramine (but not paroxetine) , 3 to 5 h before intercourse, was reported to be efficacious, although IELT improvement was inferior compared to daily treatment . so some recommend on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects.

Dapoxetine

- It is a potent SSRI, it is an on-demand oral treatment for PE.
- It is quickly absorbed with a Tmax of 1.5 h and is rapidly cleared.
- Dapoxetine, 30 and 60 mg, was administered 1 to 3 h before intercourse.

IV. Phosphodiesterase type 5 inhibitors

Mechanism of action remain unclear

- reduce performance anxiety due to better erections
- down-regulate the erectile threshold to a lower level of arousal so that greater arousal is required to achieve the ejaculation threshold.

sildenafil combined with SSRI is superior to SSRI monotherapy.

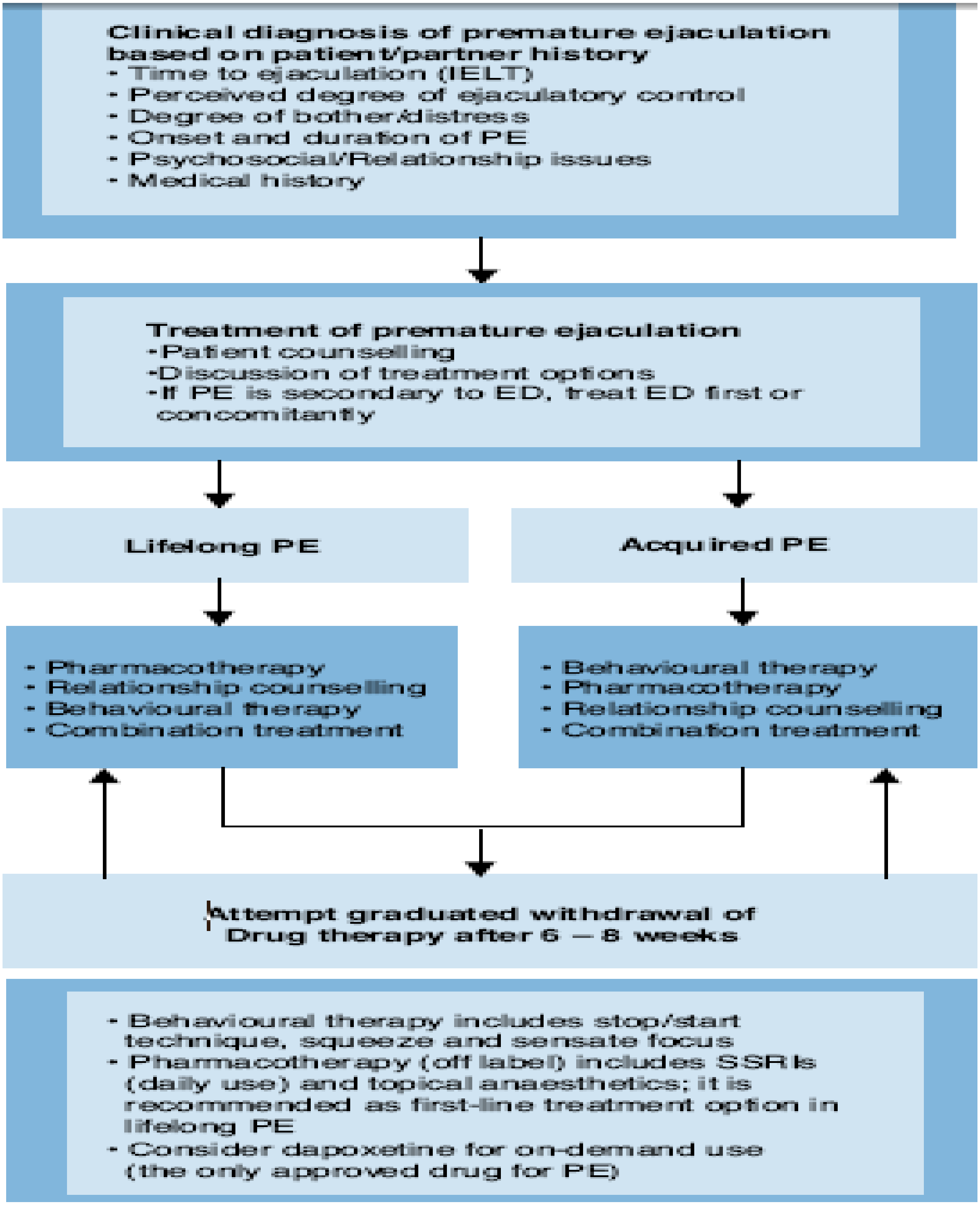
There are limited data on the efficacy in PE of other PDE5 inhibitors (tadalafil and vardenafil) .

Other drugs

- Adrenergic blockade aims to decrease the sympathetic tone of the seminal tract and therefore delay ejaculation
- Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline.

Recommendation

- Before beginning treatment, Erectile dysfunction, in particular, or other sexual dysfunction or genitourinary infection (e.g. prostatitis), should be treated first or at the same time as PE
- Various behavioural techniques have demonstrated benefit in treating PE and are indicated for patients uncomfortable with pharmacological therapy.
- In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner and can be difficult to do. In addition, long-term outcomes of behavioural techniques for PE are unknown.
- Recurrence is likely after treatment cessation.
- Behavioural therapy may augment pharmacotherapy to enhance relapse prevention



Clinical diagnosis of premature ejaculation based on patient/partner history
- Time to ejaculation (IELT)
- Perceived degree of ejaculatory control
- Degree of bother/distress
- Onset and duration of PE
- Psychosocial/Relationship issues
- Medical history

Treatment of premature ejaculation
- Patient counselling
- Discussion of treatment options
- If PE is secondary to ED, treat ED first or concomitantly

Lifelong PE
- Pharmacotherapy
- Relationship counselling
- Behavioural therapy
- Combination treatment

Acquired PE
- Behavioural therapy
- Pharmacotherapy
- Relationship counselling
- Combination treatment

Attempt graduated withdrawal of Drug therapy after 6 – 8 weeks

- Behavioural therapy includes stop/start technique, squeeze and sensate focus
- Pharmacotherapy (off label) includes SSRIs (daily use) and topical anaesthetics; it is recommended as first-line treatment option in lifelong PE
- Consider dapoxetine for on-demand use (the only approved drug for PE)